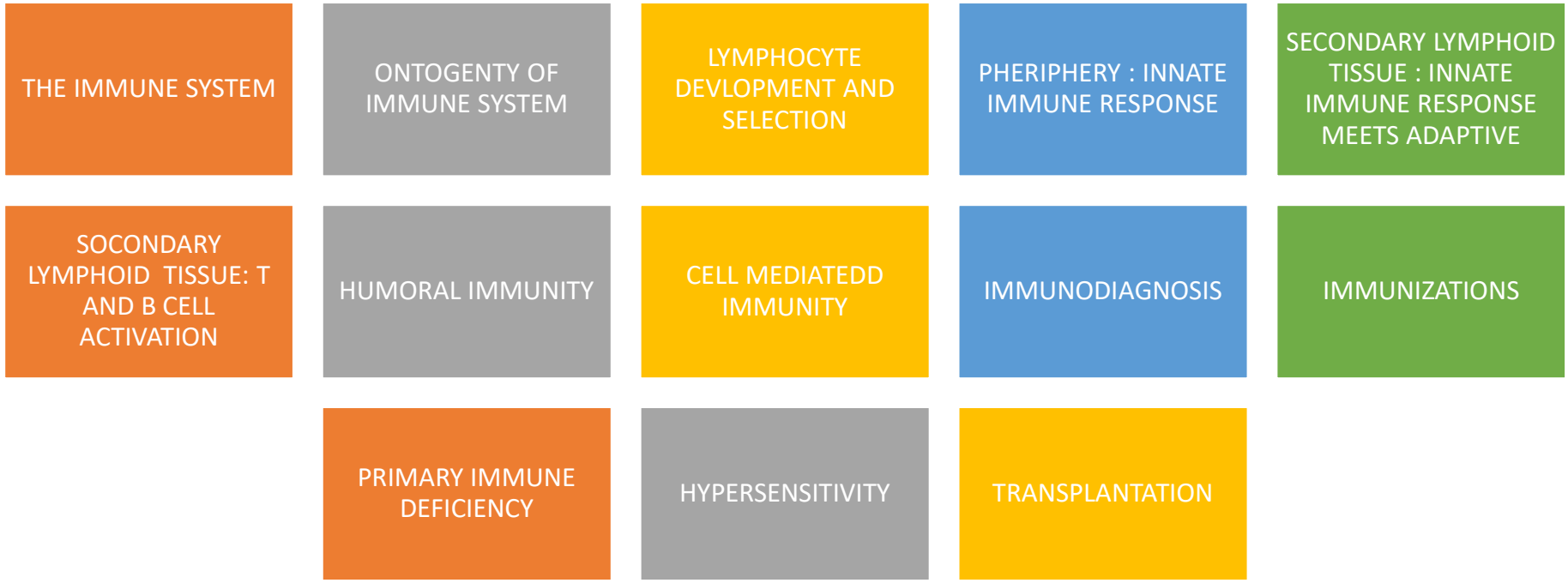
IMMUNOLOGY


THE IMMUNE SYSTEM
ONTOGENTY OF IMMUNE SYSTEM
LYMPHOCYTE DEVLOPMENT AND SELECTION
PHERIPHERY : INNATE IMMUNE RESPONSE
SECONDARY LYMPHOID TISSUE : INNATE IMMUNE RESPONSE MEETS ADAPTIVE
SOCONDARY LYMPHOID TISSUE: T AND B CELL ACTIVATION
HUMORAL IMMUNITY
CELL MEDIATEDD IMMUNITY
IMMUNODIAGNOSIS
IMMUNIZATIONS
PRIMARY IMMUNE DEFICIENCY
HYPERSENSITIVITY
TRANSPLANTATION

Immunology

IMMUNOLOGY

HUMORAL IMMUNITY

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Learning Objectives

- Explain information related to the primary humoral response
- Answer questions about antibodies of secondary immune responses

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PRIMARY HUMORAL RESPONSE

- The first isotype of immunoglobulin that can be produced by a B cell with or without T-cell help is IgM. Th s is because coding for the constant domains of the heavy chain of IgM (m chains) are the first sequences downstream from the coding for the idiotype of the molecule.
- The IgM molecule on the surface of the B cell is a monomer, but the secreted form of this molecule is a **pentamer**, held together in an extremely compact form by a **J chain** synthesized by the cell.

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Primary Humoral Response

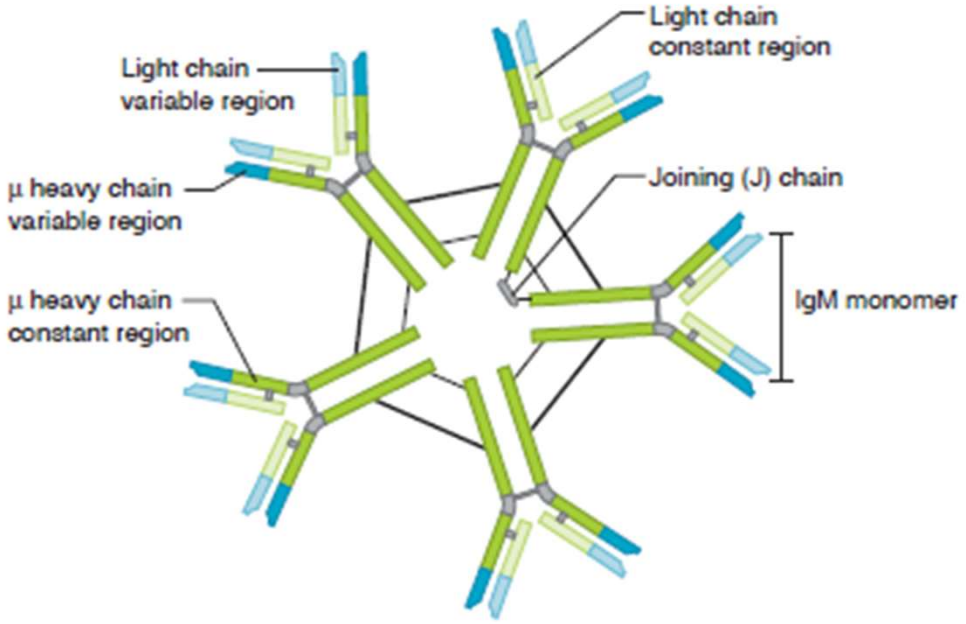

Figure I-7-1. IgM Pentamer

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IgM

The design of the IgM pentamer maximizes its effect critical to the body early during antigenic challenge. Because of its multimeric structure (5 of the Y Shaped monomers joined into one unit), plasma IgM has 5 times the capacity for binding antigenic epitopes. The valence of the molecule is therefore 10. In other words, 10 identical epitopes can be simultaneously bound, as compared with 2 for the monomeric structure.

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IgM

This design makes IgM the most effective immunoglobulin isotype at “sponging” the free antigen out of the tissues, and proves critical—as the humoral response evolves—in trapping antigen so it can be presented to the lymphocytes that will ultimately refi e the choice of effector mechanism. Although the affinity (binding strength) of the idiotype for the epitope may not be strong early in the immune response, the IgM molecule possesses the highest avidity (number of antigen binding sites available to bind epitopes) of any immunoglobulin molecule produced in the body.

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- The multimeric structure of IgM also makes it the most effective antibody at activating complement, a set of serum proteases important in mediating inflammation and antigen removal. Serum IgM is incapable of binding to cellular Fc receptors and thus cannot act as an opsonin or a mediator of antibody- dependent cell-mediated cytotoxicity (ADCC).

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Affinity and Avidity

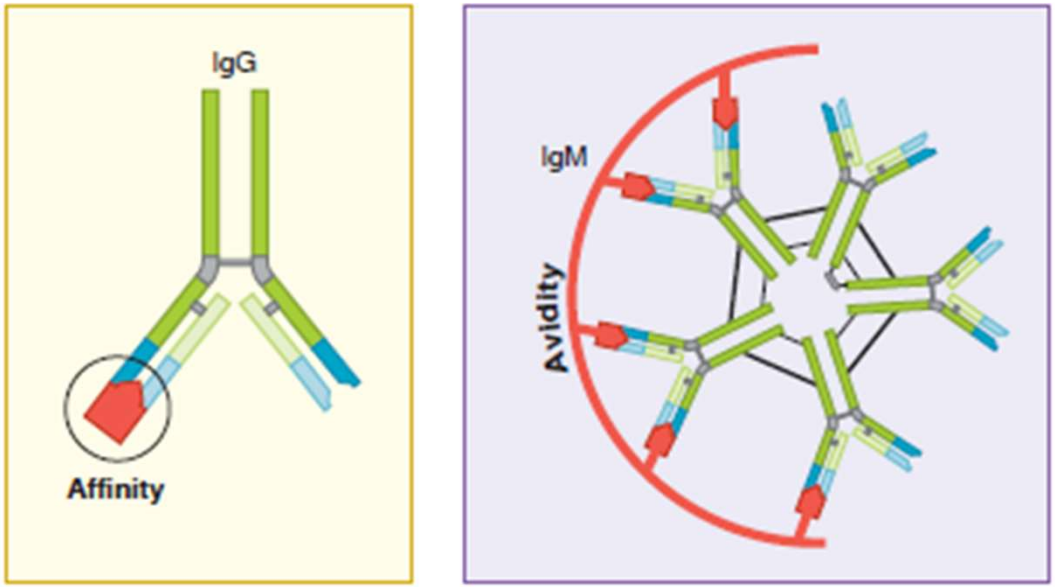

Figure I-7-2. Affinity and Avidity

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Clinical Correlate

X-linked hyper-IgM syndrome is characterized by a deficiency of IgG, IgA, and IgE and elevated levels of IgM. IgM levels can reach 2,000 mg/dL (normal 45–250 mg/dL). It is most commonly inherited as an X-linked recessive disorder, but some forms seem to be acquired and can be seen in both sexes.

• Peripheral blood of patients has high numbers of IgM-secreting plasma cells, as well as autoantibodies to neutrophils, platelets, and red blood cells.

• Patients fail to make germinal centres during a humoral immune response.

• Children with this condition suffer recurrent respiratory infections, especially those caused by *Pneumocystis Jirovecii.* The defect in this syndrome is in the gene encoding the CD40 ligand, which maps to the X chromosome. Therefore, Th cells in these patients will fail to express functional CD40L on their membrane, failing to give the costimulatory signal needed for the B-cell response to T-dependent antigens. As a result, only IgM antibodies are produced. The B-cell response to T-independent antigens is unaffected.

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ANTIBODIES OF SECONDARY IMMUNE RESPONSES

Class Switching to IgG

The preponderant isotype of immunoglobulin that begins to be produced after IgM during the primary immune response is IgG. IgG is a monomeric molecule with a γ **heavy chain** and a new set of effector functions. A majority of IgG is produced in response to IFN-g produced by the Th1 cells. IgG exists in 4 different **subisotypes** (subclasses) in humans, IgG1, IgG2, IgG3, and IgG4, each of which exhibits a slightly different capacity in effector function. In general, however, IgG has the following characteristics:

- Activates complement
- Acts as an opsonin, enhancing phagocytosis
- Neutralizes pathogen and toxins
- Mediates ADCC IgG is also actively transported across the placenta by receptor-mediated transport and thus plays a crucial role in protection of the fetus during gestation.

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Basic Structure of IgG

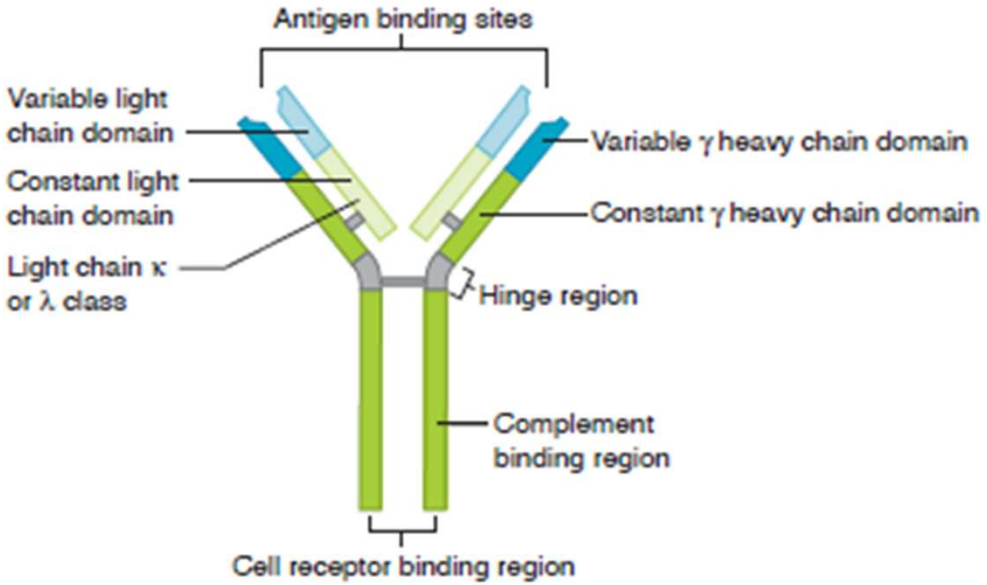

Figure I-7-3. Basic Structure of IgG

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Class Switching to IgA

Another isotype of antibody that can be produced following class switching is IgA, though it is more commonly produced in the submucosa than in the lymph nodes and spleen. IgA generally exists as a **dimer**, held together by a J chain similar to that produced with IgM. IgA has the following characteristics:

- Serves as a major protective **defence of the mucosal surfaces of the body**
- Any pathogen that infects the mucosa will induce IgA production by the secretion of TGF-b by infected cells and to a lesser extent, IL-5.
- Functions as a neutralizing antibody by inhibiting the binding of toxins or pathogens to the mucosa of the digestive, respiratory, and urogenital systems (sole function)
- Does not activate complement, act as an opsonin, or mediate ADCC
- Exists in 2 isotypes, IgA1 and IgA2

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The Classical Pathway

The **classical pathway** is activated by antigen-antibody complexes and is probably the more phylogenetically advanced system of activation. Both IgG and IgM can activate the system by this pathway, although IgM is the more efficient. Although the complement cascade is considered a component of the innate immune response, its overlapping stimulation of effector functions of cells of the adaptive immune response, as well as its role in enhancement of inflammation, make it a critical effector system for removal of extracellular invaders and concentration of antigens into the secondary lymphoid organs, where the adaptive immune responses are elicited.The homing of specific memory cells to epithelial and mucosal surfaces leads to the production of specialized lymphoid aggregations along these barriers. Collectively referred to as **mucosal-associated lymphoid tissues** (MALT), they include the tonsils and Peyer patches, as well as numerous, less well-organized lymphoid accumulations in the lamina propria. Th2 cells in these sites are dedicated to providing help for class switching to IgA. Most IgA-secreting B lymphocytes and plasma cells in the body will be found in these locations.

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Secretory IgA

(that which is released across the mucosa of the respiratory, digestive, and urogenital tracts) differs from serum IgA in an important fashion. As the IgA dimer is produced by plasma cells and B lymphocytes, it becomes bound to poly-Ig receptors on the basolateral side of the epithelia, is endocytosed, and is released into the lumen bound to a secretory piece that is the residue of the receptor. The **secretory component** thus serves an important function in transepithelial transport, and once in the lumen of the tract, has a function in protecting the molecule from proteolytic cleavage.

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Class Switching to IgE

IgE binds directly to Fcε receptors present on mast cells, eosinophils and basophils, and is involved in elicitation of protective immune responses against parasites and allergens. It does not activate complement or act as an opsonin. Its heavy chain is called the ε chain.

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Antibodies Subtypes

Table I-7-1. Biologic Functions of the Antibody Isotypes

	IgM	IgG	IgA	IgD	IgE
Heavy chain	μ	γ	α	δ	ε
Adult serum levels (in mg/dL)	45–250	620–1,400	80–350	Trace	Trace
Functions					
Complement activation, classic pathway	+	+	–	–	–
Neutralization	+/–	+	+	–	–
Opsonization	–	+	–	–	–
Antibody-dependent cell-mediated cytotoxicity (ADCC)	–	+	–	–	+/–
Placental transport	–	+	–	–	–
Naïve B-cell antigen receptor	+	–	–	+	–
Memory B-cell antigen receptor (one only)	–	+	+	–	+
Trigger mast cell granule release	–	–	–	–	+

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Clinical Correlate

Immunodeficiencies Involving B Lymphocytes

Patients with B-cell deficiencies usually present with recurrent pyogenic infections with extracellular pathogens. The absence of immunoglobulins for opsonization and complement activation is a major problem.

- T-cell immune system is intact.
- T-cell activities against intracellular pathogens, delayed-type hypersensitivity, and Tumor rejection are normal (*see* chapter 8).

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Chapter Summary

• IgM is the first isotype of antibody that can be produced. It exists in serum as a pentamer held together by a joining (J) chain

• The functions of IgM are (as a monomer) receptor on B cells, antigen capture in the secondary lymphoid organs, and (as a pentamer) in plasma, activation of complement.

• IgG is the major isotype produced after IgM. It exists in 4 sub isotypes. It activates complement, opsonizes, mediates ADCC, and is actively transported across the placenta.

• IgA is the major isotype produced in the submucosa, colostrum, and breast milk. It is a dimer with a J chain holding it together. It functions in inhibiting the binding of substances to cells or mucosal surfaces. It does not activate complement or mediate opsonization.

• Secretory IgA is transported into the lumen of the gastrointestinal, respiratory, or genitourinary tracts by binding to a polyimmunoglobulin receptor.

• This receptor (now called a secretory component) is retained for protection of IgA from proteolytic cleavage.

• IgE is the antibody that binds to mast cells and is responsible for anthelminthic and allergic responses.